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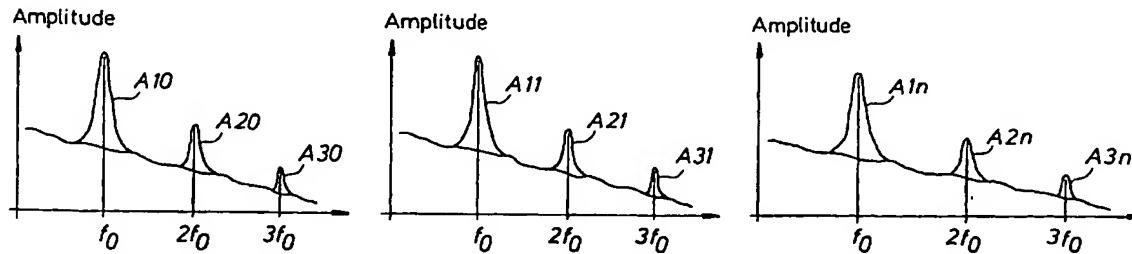
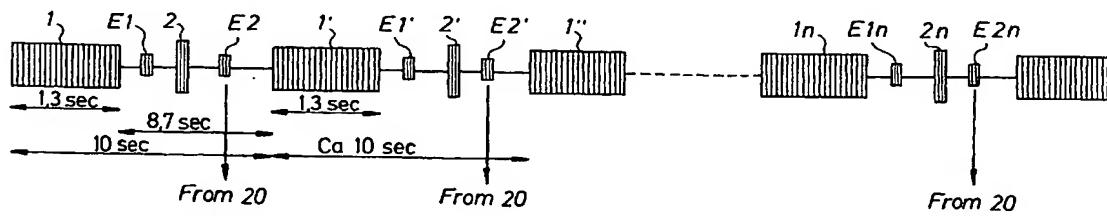
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD AND APPARATUS FOR NON-INVASIVE MEASUREMENT OF A TEMPERATURE CHANGE INSIDE A LIVING BODY



(57) Abstract: Method and apparatus for non-invasive measuring of the temperature change of a target inside a body by transmitting an ultrasonic pulse to the target, subjecting a pulse reflected from the target to frequency analysis, and calculating the temperature change of the target therefrom. A frequency spectrum of the reflected pulse is produced and the calculation of the temperature change is effected on the basis of harmonics appearing in said spectrum.

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Title of the Invention

Method and apparatus for non-invasive measurement of a temperature change inside a living body.

Background of the invention***Field of the invention***

The invention relates generally to method and apparatus for non-invasive measurement of a change of the temperature inside a living body, from the outside or a cavity of the living body.

When an ultrasound wave passes through a material such as body tissue energy of the ultrasonic wave is absorbed and the wave is attenuated. The part of the ultrasonic wave that is absorbed is converted substantially to heat energy. Therapeutic ultrasound i. e. high intense ultrasound is used for heat treatment of i. a. muscles and other structures in the living body mostly in order to increase the blood flow through the structure and to speed up the healing thereof. The heating by therapeutic ultrasound is effected up to about 3 W/cm^2 . The temperature of the heated structure and the surrounding tissue is not controlled. Recently the MR-technique has been used, but it is an expensive a slow technique. Therefore, in this case as when tissue is destructed by local heating to a temperature of 42 to 95° or when a stent inserted into a blood vessel is heated for heat treatment of abnormalities in

the vessel reliable control of the temperature change in the tissue or the stent during the treatment is desired in order to effect the treatment without injuring tissue surrounding the region to be treated by ultrasound heating.

Description of the Prior Art

It is known in the art to provide temperature control during non-invasive treatment of a target area inside a living body. Thus, JP-A-1233337 describes method and apparatus for measuring temperature of an object which cannot be approached from the outside, such as tissue inside a human body, which is heated by external heater, wherein an ultrasonic wave is transmitted to the object. A reflected wave therefrom is subjected to A/D conversion and the sensed wave is cut out at each one wavelength for frequency analysis. The temperature of the object is calculated therefrom on the basis of a predetermined relationship between a peak frequency of a frequency distribution obtained by the analysis, or a half-width thereof, and the temperature of the object.

US-A-5 370 121 describes method and apparatus for non-invasively measuring a temperature change between two points in a region of interest in the inside of a living subject which is treated with heating radiation. A first ultrasound wave form, containing at least one ultrasound pulse is emitted into the subject at a first point of time and is incident on the region of interest which reflects a corresponding first set of echo signals from which a first ultrasound image is

generated and stored. A second ultrasound waveform identical to the first ultrasound wave form is emitted into the subject at a second point in time incident on said region which reflects a corresponding second set of echo signals. A second ultrasonic image is generated therefrom. From the first and second ultrasonic images a differential ultrasound image is generated. A temperature change, if any, in the region of interest is identified during the course of producing ultrasound images of the region by determining the change of the acoustic impedance of the region of interest between the first and second points in time, a temperature change being allocated to the impedance change.

US-A-4 807 633 describes method and apparatus for non-invasive thermometry which is based on the observation that attenuation of a transmitted or reflected beam of ultrasound in tissue changes measurably as tissue temperature changes. The prior art method and apparatus comprise periodic amplitude measurement of back-scattered ultrasound.

US-A-6 050 943 relates to a combined imaging, therapy and temperature monitoring system comprising an acoustic transducer assembly configured to enable the ultrasonic system to perform the imaging, therapy and temperature monitoring functions. The transducer assembly includes a single transducer which is operatively connected to an imaging subsystem, a therapy subsystem and a temperature monitoring subsystem. The therapy subsystem can generate high power acoustic energy to heat a treatment region, and the temperature monitoring subsystem can map and

monitor the temperature of tissue in said region and display the temperature on a display. Mapping of the temperature distribution in tissue in the treatment region is accomplished by measuring the time-of-flight and amplitude data of acoustic pulses through said region while exploiting the temperature dependence of the speed of sound and acoustic attenuation in the tissue of the treatment region. Imaging, temperature heating and temperature monitoring of the treatment region can be conducted substantially simultaneously.

US 4 566 460 describes method and apparatus for measuring a non-linear parameter A/B of an acoustic medium or its distribution, and the application of the parameter to non-invasive measurement of internal temperature of a sample. A continuous wave ultrasonic probing beam is radiated through the sample, and a pumping wave which is an ultrasonic pulse is superposed on the probing beam. A phase change in the probing beam caused by the pumping wave is detected and from this phase change the non-linear parameter (B/A) is obtained. From the information concerning the variation of the measured value of said parameter the inner temperature of the sample is obtained.

US 5 360 268 describes an ultrasonic temperature measuring apparatus measuring the temperature of a medium, which includes a transmitter for transmitting ultrasonic waves and a receiver for receiving the ultrasonic waves and providing a received signal. An operation unit calculates the propagation time of the ultrasonic waves, and the temperature in the medium is

determined according to the propagation time of the ultrasonic waves.

US 4 817 615 describes an ultrasonic diagnostic apparatus which includes an ultrasonic transducer for transmitting an ultrasonic wave into a body to be examined and receiving the reflected ultrasonic wave, phase variations being detected to obtain fluctuation of the temperature within the body.

A similar ultrasonic pulse temperature determination method and apparatus are described in US 4 754 760 wherein ultrasound pulses are transmitted into a specimen and the attenuation of the ultrasound pulses between different depths in the specimen is determined before and after heating of the specimen. The change in temperature of the specimen is determined from the obtained attenuation values.

JP 61280533 describes an apparatus for measuring internal temperature of a living body by reflected ultrasonic wave delivered to the interior of the living body. Spectral analysis is applied to the frequency of the reflected wave and the change quantity of the frequency spectrum of the reflected wave is calculated and is converted to a temperature change quantity.

The prior art methods and apparatuses do not provide the precision in measuring the temperature of the target as is required in order to provide an accurate temperature control for an adequate therapeutic treatment, and/or require use of several measuring points, which makes the use of the prior art methods and apparatuses rather complicated.

Brief Summary of the Invention

The object of the invention is to overcome the drawbacks mentioned above and to provide method and apparatus for accurate measuring of the temperature in a very small area of a target within a region which is ultrasonically heated, especially for treating a vessel using stent material or for destructing tissue such as cancer tissue, by using back scattered ultrasound from the target for the temperature measurements.

More particularly the invention provides method and apparatus allowing control of the temperature in a target heated by pulsed therapeutic high intense ultrasound, after each therapeutic pulse in order to produce a well adjusted energy dose for creating an adequate temperature of a confined small area of the target.

In order to achieve the above object the invention provides a method according to claim 1 and an apparatus according to claim 9.

Further features of the invention are defined in the dependent claims.

Brief Description of the Drawing

FIG 1 is a block diagram of an apparatus of the invention,

FIG 2 is a time diagram of the procedure applied when using the apparatus of **FIG 1**,

FIG 3 is a frequency spectrum of a pulse of back scattered ultrasound, and

FIGS 4 and 5 are diagrams illustrating the frequency peaks of the harmonics of the back scattered pulse.

Detailed Description of the Invention

Referring to FIG 1 the apparatus for practising the method of the invention comprises a control unit 10 including a transmitter 11 for generating low intense (diagnostic) ultrasound energy for temperature measuring, and a transmitter 12 for generating high intense therapeutic ultrasound energy, the ultrasound energy being transmitted by a transducer 13 comprising a number of ultrasound emitters formed by thin ceramic plates 14 mounted to a reflecting bowl shaped mounting system 15 focusing the transmitted ultrasound energy. The two transmitter circuits can also be combined to form a single circuit for therapeutic as well as diagnostic purposes. Therapeutic ultrasound energy generated by the transmitter 12 is emitted from the transducer 13 which is applied against an outside surface of the body tissue, for treatment of the tissue in a target region T of body tissue e. g. cancer tissue, to be treated, or to a stent located in a blood vessel. It is also possible to use phased array transducer systems both for treating and temperature measuring instead of the described bowl shaped transducer arrangement. The target region T is located between first and second tissue surfaces A and B. The thickness of the target region T between surfaces A and B is defined by applying one or the other of prior art

methods developed for said purpose. Transducer 13 is adjusted in focus the emitted ultrasound energy on an area F located in the target region T. In FIG 1 the focused area F in the target region T has an ellipsoid form of a size which is substantially the same as that of a grain of rice but can be smaller or larger depending on the construction. A sensor 17 is provided in transducer 13 for picking up back scattered ultrasound echo signals. A receiver 18 including a wide band amplifier with controlled amplification is provided for receiving and amplifying the picked up ultrasound echo signals. Receiver 18 is connected to an analogue/digital converter 19 with memory and with a high sampling frequency f_s ranging from $> 3 \times f_0$ to about $20 \times f_0$ where f_0 is the fundamental frequency (first harmonic) of the echo signal, for converting signals received by the receiver from analogue form to digital form in order to facilitate subsequent signal processing. f_0 can be of different frequency with a variation in bandwidth for optimal temperature sensitivity. Output signals from the receiver are transmitted via the converter to an analyser 20 which can be an FFT (fast Fourier transform) analyser or a Doppler analyser or wavelet technique or an analyser correlating echoes from different types and configuration of transmitted ultrasound pulses. A single analyser of one of the types mentioned or a combination thereof can be provided. The output signal from the analyser (or each analyser) is transferred to a complex comparing circuit 21 herein referred to as a comparator wherein the signal is compared with a

reference stored therein. As an optional (used or not used) feature comparator 21 is operatively connected to transmitter 10. When a comparison indicates that the input signal equals a pre-set reference value the comparator shuts off transmitter 12. Analyser 20 is connected to a calculator 22 including programs for processing the received back scattered echo signals. A display 23 is connected to comparator 21 and a calculator 22 for visually presenting the parameters of interest.

Parameters of the treatment such as ultrasound intensity, type of pulse sequence, depth of target region T, frequency of the ultrasound, and selected temperature are programmed or set on control unit 10 and measure the temperature in every focal point.

With reference to FIG 2 which illustrates diagrammatically a typical sequence for effecting a non-invasive treatment by means of therapeutic high intense ultrasound the several steps being marked on a time axis.

A therapeutic ultrasound pulse 1 is emitted from the apparatus for about 1.3 seconds and then there is a pause to the next therapeutic ultrasound pulse 1' for a period of 8.7 seconds. This can also be scaled down by approximately a factor of 10, and also the pulse duration quote can be changed. During the pause of 8.7 seconds between pulses 1 and 1' a temperature diagnostic pulse 2 from transmitter 11 is emitted by transducer 13 and the result of the treatment is checked by using the back scattered echo E2 from pulse 2 and the back scattered echo E2' from pulse 2' or,

generally, by using the back scattered echo E_{2n} from pulse $2n$.

The signal representing the back scattered echo from the target region T under treatment by means of the therapeutic high intense ultrasound is presented as a frequency spectrum as disclosed in FIG 3 by analyser 20. This spectrum comprises a first harmonic (fundamental frequency) A_1 , a second harmonic A_2 , a third harmonic and possibly further high order harmonics. The first, second and third harmonics have the frequency f_0 , $2f_0$ and $3f_0$, respectively. The amplitudes of these frequencies is represented by analyser 20 as shown in FIG. 2.

Measurement of echo E_2 is the first measurement and is designated 0, and the amplitude of three harmonics included in said echo are designated A_{10} at the frequency f_0 , A_{20} at the frequency $2f_0$, and A_{30} at the frequency $3f_0$.

The measurement of echo E_2' is the second measurement and is designated 1. The corresponding three harmonics are designated A_{11} , A_{21} and A_{31} .

At measurement n of an echo caused by a diagnostic temperature measurement pulse $2n$ the three harmonics are designated A_{1n} , A_{2n} and A_{3n} .

The echo of the tracking end of the therapeutic pulse 1, $1'$ and $1n$ are indicated in FIG. 2 at E_1 , E_1' and E_{1n} and can be used as measurement pulses but it is preferred to use separate pulses 2, $2'$ and $2n$ for this purpose. Referring to FIG. 2 the first simplest quotient is calculated for each measuring point at E_1 and E_2 and for the E_{1n} and E_{2n} by the formula:

quotient = (Amplitude of second harmonic/Amplitude of first harmonic)

or

quotient = (Intensity integral of second harmonic/Intensity integral of first harmonic)

as illustrated in FIG. 3.

By means of a program in the calculator 22 the quotient,

$$\frac{A_{1n} - A_{10}}{A_{10}}$$

is calculated, wherein A_{10} is the amplitude of the first harmonic before start of treatment and A_{1n} is the amplitude of the first harmonic at measurement n after start.

An other quotient,

$$\frac{A_{2n} - A_{20}}{A_{20}}$$

is calculated, wherein A_{20} is the amplitude of the second harmonic before start of treatment and A_{20} is the amplitude of the second harmonic at measurement and A_{2n} is the amplitude of the second harmonic at measurement n after start.

Calculations can be made for following measurements the measurement to provide the quotient for the second harmonic and the quotient between second harmonic and first harmonic

$$\frac{A_{2n} - A_{2(n-1)}}{A_{2(n-1)}}$$

were $n-1$ is the measurement just before measurement nr n . The invention is based on the findings that the amplitude quotient of harmonics (as well as intensity, quotient based on the square of the amplitude) is dependent of the temperature change in the target region during heating thereof. Thus it has been found that there is an almost linear relationship between the temperature change and the quotient

$$\Delta T = C \times \text{the quotient}$$

wherein C is a constant factor that is determined empirically and is specific for tissue type, depth of target region T , ultrasound, intensity and frequency and the sensor system applied.

With reference to FIG 4 as an alternative to the amplitude quotient an integral quotient can be used the area of the peaks in the diagram down to the horizontal axis for the amplitude zero being used for the calculation of the quotient

$$\frac{Y_{21} - Y_{20}}{Y_{20}}$$

or as shown in Fig 5 the quotient is calculated by taking into account only the area above a noise level N which in many cases can be neglected if the signal to noise ratio (SNR) is large enough. The quotients based on the FFT calculations can be based on the amplitude from the echoes or the intensities from the echoes which is the square of the amplitude. The temperature of the target area relating to the measurements made is calculated on the basis of one of said quotients or a combination of several quotients.

In experiments the inventor has based the calculations on all types of quotient using all harmonics in different combinations to find the most sensitive combination of one or many quotients. The above given examples are the most frequently used quotients. However this is tissue dependent and must be experimentally investigated from cases to cases. Depending on the result the non-invasive treatment is repeated under temperature control according to the procedure described until the desired temperature in the target area T (tissue or inserted artificial material) or a shell around the target area has been developed.

Other non-linear calculation systems can be proposed in order to increase the precision of the calculation of the temperature change such as

$$\Delta T = \text{function (quotient)}$$

wherein the function has to be determined from case to case.

In heating a stent covered by an ultrasound absorbing and reflecting material such as polytetrafluoro ethylene, polyurethane or elastomer it should be possible to measure in the range from 37 to about 55°C and in connection with treatment of cancer up to 85°C. For therapeutical treatment of e.g. muscles it is desired to measure up to 41°C in order to avoid a higher temperature.

Preferred embodiments have been described in order to illustrate the invention but it is obvious to the man skilled in the art that these embodiments are examples only and that modifications thereof can be

made without departing from the scope of the invention as defined in the claims.

CLAIMS

1. Method of non-invasive measuring of the temperature change of a target inside a body by transmitting an ultrasonic pulse to the target, subjecting a pulse reflected from the target to frequency analysis, and calculating the temperature change of the target there from, **characterized** in that a frequency spectrum of the reflected pulse is produced and that the calculation of the temperature change is effected on the basis of harmonics appearing in said spectrum.
2. The method of claim 1 wherein the calculation includes calculation of a quotient

$$\frac{A_{kn} - A_{k0}}{A_{k0}}$$

wherein A_{k0} represents the size of a frequency peak of a harmonic of number k , based on amplitude or intensity as measured at an earlier moment and A_{kn} represents the size of a frequency peak of said harmonic as measured at a later moment n .

3. The method of claim 2 wherein the temperature change is calculated according to the relationship

$$\Delta = k * \text{quotient}$$

wherein k is a constant determined empirically.

4. The method of claim 2 wherein the quotient is calculated for different harmonics represented by frequency peaks in said spectrum.

5. The method of claim 2 wherein the size of the harmonic is represented by the amplitude of the frequency peak representing the harmonic in the frequency spectrum.
6. The method of claim 2 wherein the size of the harmonic is represented by the surface defined by the frequency peak representing the harmonic in the frequency spectrum.
7. The method of claim 7 wherein the surface extends from a noise level defined by the frequency spectrum.
8. Apparatus for non-invasive measuring of the temperature change of a target inside a body comprising means for transmitting an ultrasonic pulse to the target, means for receiving a pulse reflected from the target means for frequency analysis of the reflected pulse, and means for calculating the temperature change of the target therefrom, **characterized** by means for producing a frequency spectrum of the reflected pulse, and means for calculation of the temperature change on the basis of harmonics appearing in said spectrum.

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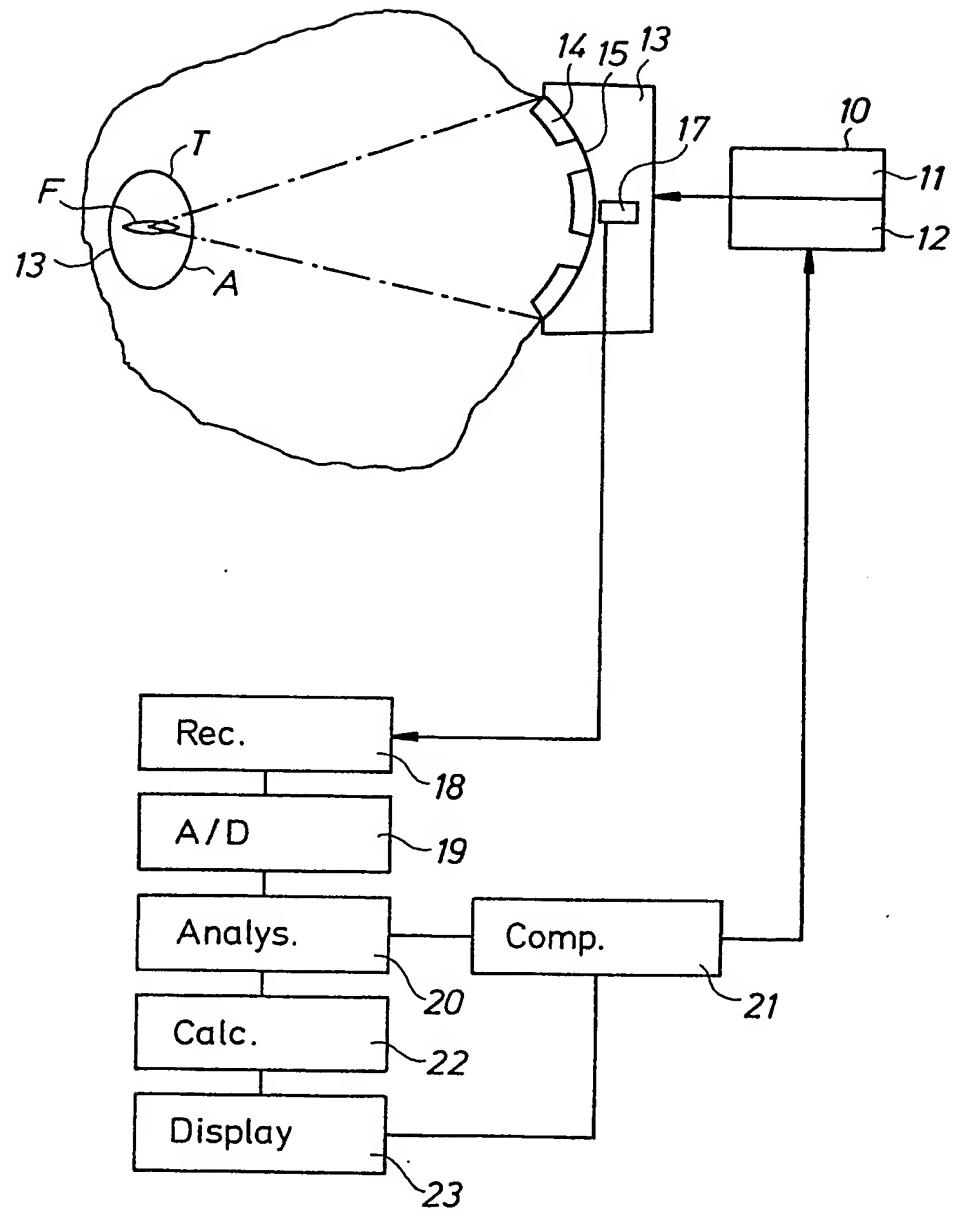


FIG. 1

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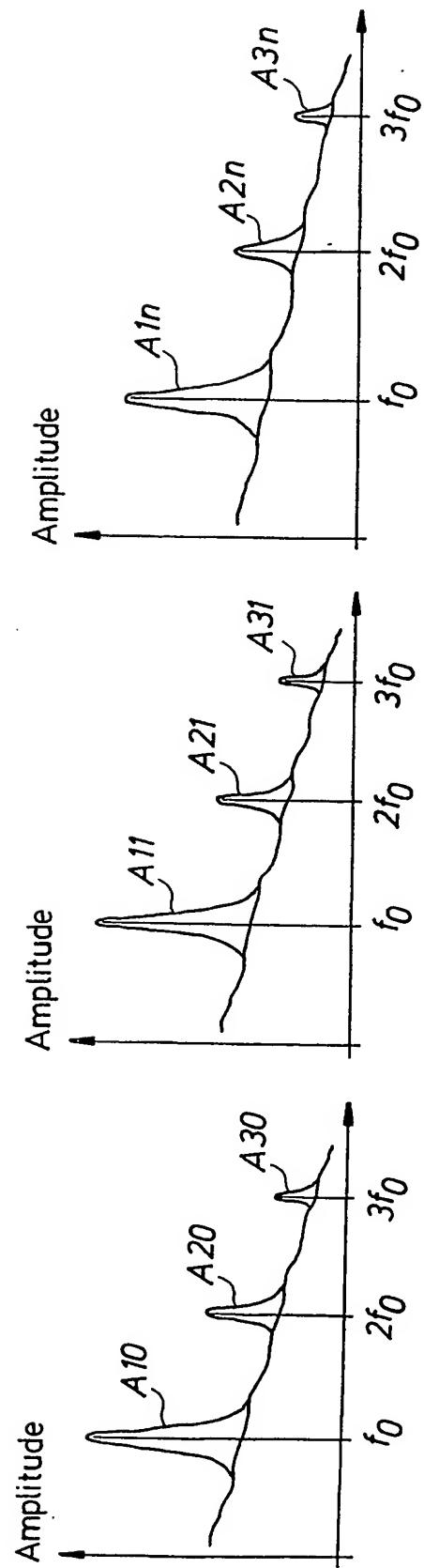
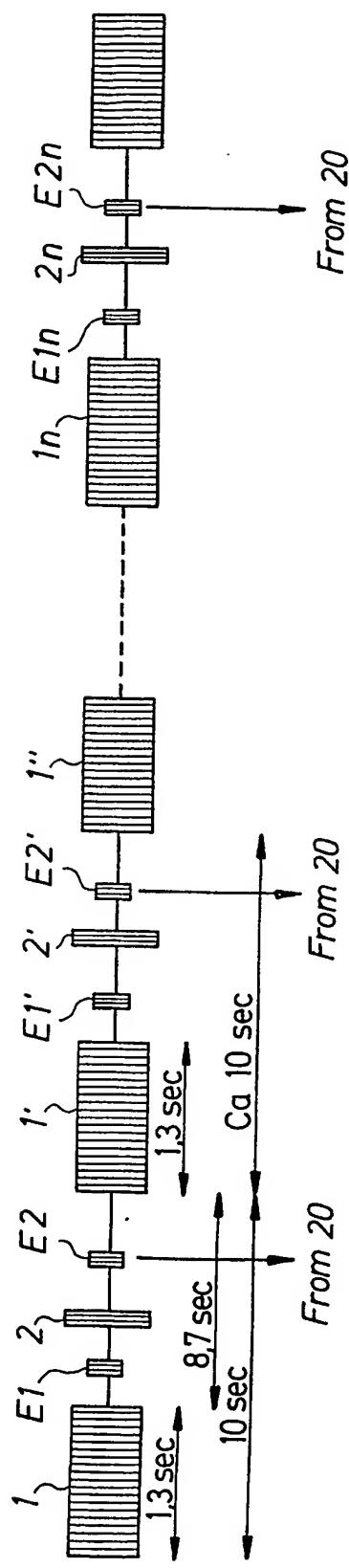


FIG. 2

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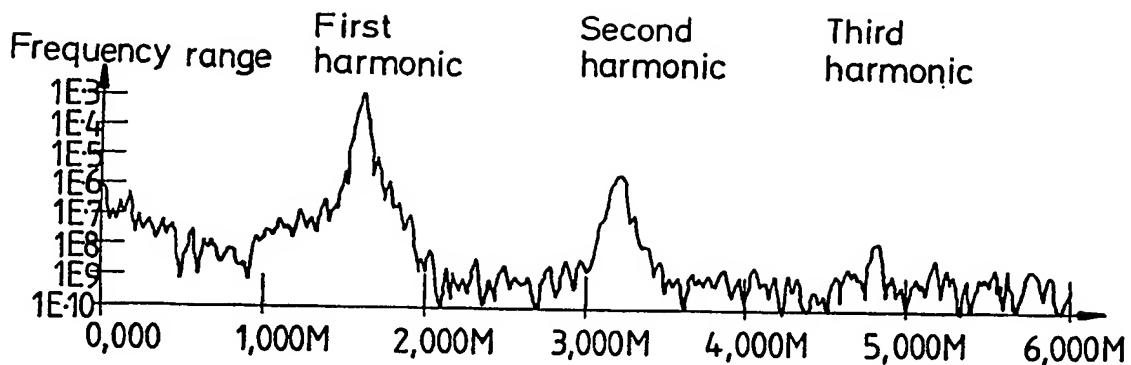


FIG. 3

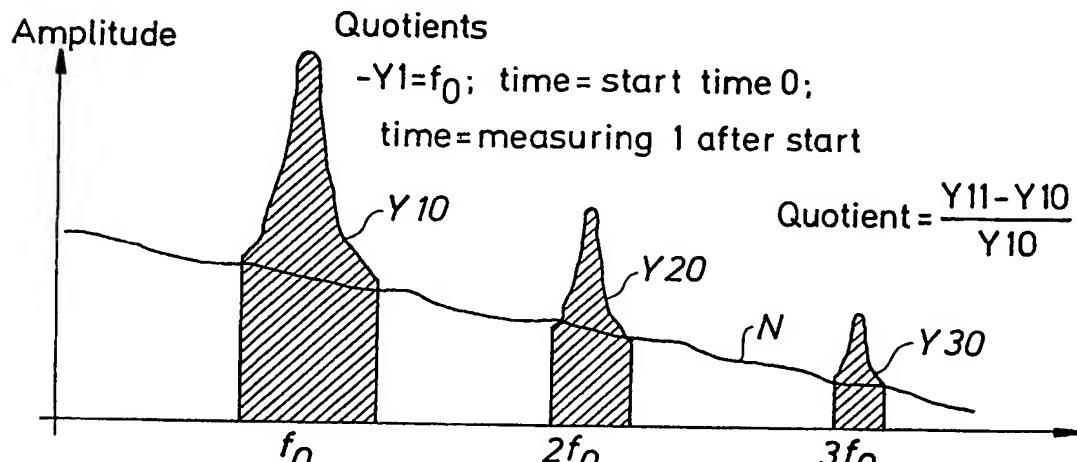


FIG. 4

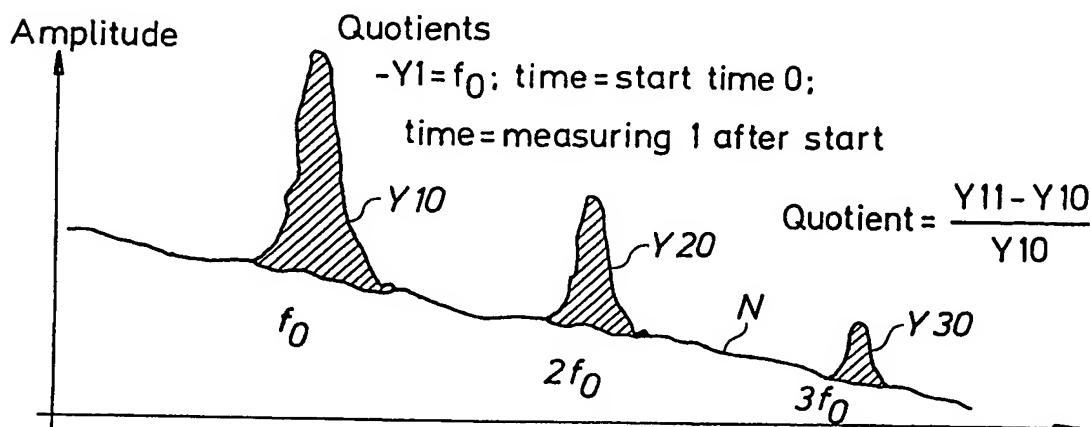


FIG. 5

INTERNATIONAL SEARCH REPORT

Application No

PCT/SE 03/01783

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61B8/00 G01K11/26 A61N7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61B G01K A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

PAJ, EPO-Internal, WPI Data, INSPEC, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 013, no. 557 (P-974), 12 December 1989 (1989-12-12) & JP 01 233337 A (NIPPON TELEGR & TELEPH CORP), 19 September 1989 (1989-09-19) abstract --- US 4 807 633 A (FRY FRANCIS J) 28 February 1989 (1989-02-28) abstract; figure 1 -----	1-18
A		1-18

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

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15 March 2004

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE 03/01783**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-8 because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 1-8

Claim(s) 1-7 relate(s) to a method of treatment of the human body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless a search has been executed for these (this) claim(s). The search has been based on the alleged effects of the compound(s)/product/device.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Application No
PCT/SE 03/01783

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
JP 01233337	A 19-09-1989	JP 1922847	C	07-04-1995
		JP 6050264	B	29-06-1994
US 4807633	A 28-02-1989	NONE		